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EXAMINER

DAVIS, MINH TAM B

ART UNIT PAPER NUMBER

1642

DATE MAILED: 06/05/2003

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n No.

09/942,940

Applicant(s)

KOO ET AL.

Examin r

MINH-TAM DAVIS

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 March 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 2,3,8,11,12,17 and 18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4-7,9,10,13-16 and 19-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4, 7.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Applicant's election with traverse of Group V, claims 1, 4-7, 9-10, 13-16, 19-21 in Paper No. 6 is acknowledged. The traversal is on the ground(s) that 1) Each of the 3 small organic molecule inhibitors should be species since claims 4, 13 and 19 are sub-generic and read on a small organic molecule inhibitor, 2) Similarly, the proteinaceous MAPK pathways inhibitors are claimed as the subgenus "MEK directed proteases", e.g., claims 12, 11 or 17, wherein the B. anthracis lethal factor and Yersinia protein are species of this subgenus, and 3) Ultimately, the 3 small organic molecule inhibitors and the protein based MAPK pathway inhibitors all are species of the generic claims to "MAPK pathway inhibitors" as claimed in claims 1, 8, 9 and 16. This is not found persuasive because claims 1, 8, 9 and 16 are generic linking claims, and thus the 3 small organic molecule inhibitors and the protein based MAPK pathway inhibitors would only be considered as species at the time of allowance, if claims 1, 8, 9 and 16 are allowable, according to MPEP 804.01.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, group V, claims 1, 4-7, 9-10, 13-16, 19-21, wherein claims 1, 4-7, 9-10, 13-16, 19-21 are examined only to the extent of a method of treating melanoma, using the organic small molecule PD184352.

OBJECTION

1. Claims 1, 9, 16 are objected to for using the abbreviated language "MAPK pathway".

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2. Claim 9 is objected to because claim 9 is confusing. It is not clear what the sum of "the products" are.

3. Claim 9 is objected to for the use of the language "characterized". It is not clear how the response is "characterized". This objection could be obviated if the claim is amended, for example, to replace "characterized" with "comprising"

4. Claim 15 is objected to because claim 15 depends on non-elected claims 11-12.

5. Claim 21 is objected to because claim 21 depends on non-elected claims 17-18.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 1, 4, 6-7, 9-10, 13, 15-16, 19, 21 are rejected under 35 USC 112, first paragraph.

Claims 1, 4, 6-7, 9-10, 13, 15-16, 19-21 are drawn to a method for killing melanoma cells, or inducing an antitumor response in a mammal having melanoma, or inhibiting growth or recurrent growth of a melanoma tumor in a mammal having melanoma, comprising administering "an inhibitor of the MAPK pathway", or "an organic small molecule" which induces apoptosis in said cells, or which is cytotoxic to melanoma cells

The specification discloses that *in vitro*, the MEK-directed protease Lethal factor, and the small organic molecules PD184352 and PD98059 induces apoptosis in various human melanoma cell lines (Example II, and table 5 on page 49). Although the specification includes other MAPK inhibitors such as the small molecule U0126, or p38 kinase inhibitor SB 203580 (p.20, first paragraph), one cannot determine whether these molecules induce apoptosis or are cytotoxic to melanoma cells.

It is noted that the structure of the three disclosed inhibitors of the MAPK pathway i.e. Lethal factor, and the small organic molecules PD184352 and PD98059 that induce apoptosis or are cytotoxic to melanoma cells is completely unrelated to each other.

The claims, as written, however, encompass a method for killing melanoma cells, or inducing an antitumor response in a mammal having melanoma, or inhibiting growth or recurrent growth of a melanoma tumor in a mammal having melanoma, comprising administering "any inhibitor of the MAPK pathway", or "any organic small molecule" which induces apoptosis in said cells, or which is cytotoxic to melanoma cells, wherein the inhibitor of the MAPK pathway, or the organic small molecule which induces apoptosis in said cells, or which is cytotoxic to melanoma cells could have any structure.

The instant disclosure of three species of inhibitor of the MAPK pathway or two species of small organic molecules, the structure of which is completely unrelated to each other does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera of inhibitors of the MAPK

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pathway, or small organic molecules, that induce apoptosis or are cytotoxic to melanoma cells.

Although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of inhibitors of the MAPK pathway, or small organic molecules, that induce apoptosis or are cytotoxic to melanoma cells. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to

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enable one of skill to isolate and identify the inhibitors of the MAPK pathway, or small organic molecules, that induce apoptosis or are cytotoxic to melanoma cells encompassed and no identifying characteristic or property of the instant inhibitors of the MAPK pathway, or small organic molecules, that induce apoptosis or are cytotoxic to melanoma cells is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of a lethal factor and two small organic molecules all having completely unrelated structure, is insufficient to describe the genus inhibitors of the MAPK pathway, or small organic molecules, that induce apoptosis or are cytotoxic to melanoma cells. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed. Thus, only a method for killing melanoma cells, or inducing an antitumor response in a mammal having melanoma, or inhibiting growth or recurrent growth of a melanoma tumor in a mammal having melanoma, comprising administering an inhibitor of the MAPK pathway, which is the organic small molecule PD184352, but not the full breadth of the claims meet the written description provisions of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 1, 4-7, 9-10, 13-16, 19-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains

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subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 4-7, 9-10, 13-16, 19-21 are drawn to a method for killing melanoma cells, or inducing an antitumor response in a mammal having melanoma, or inhibiting growth or recurrent growth of a melanoma tumor in a mammal having melanoma, comprising administering an inhibitor of the MAPK pathway, which is the organic small molecule PD184352.

The specification discloses *in vivo* treatment of melanoma (p.56-57). However, it is not clear that the results on pages 56-57 are from treatment using the MEK proteases or small molecule MEK inhibitors, or both at the same time. Further, no disclosure of which small molecule inhibitor is used for the treatment is found in the specification, nor any actual treatment data using PD184352 alone is found. Further, although the specification discloses the dosage of the lethal factor (LF) protein for *in vivo* killing melanoma cells (p.56), no disclosure is found for the dosage of the organic small molecule PD184352 necessary for the treatment.

The specification further discloses that *in vitro*, the small organic molecules PD184352 and PD98059 induces apoptosis of human melanoma cells (table 5 on page 49), and inhibits ERK1/2 (or MEK), enzymes of the MAPK pathway (p.1, 12). The specification however discloses that greater inhibition of ERK1 by a combination of PD98059 and IBMX, a phosphodiesterase inhibitor, actually do not induce apoptosis (p. 48 and figures 8-9).

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Thus it seems that only a certain specific level of reduction of ERK1/2, enzymes of the MAPK pathway, but not any level of reduction of ERK1/2, is correlated with *in vitro* apoptosis.

One cannot extrapolate the teaching in the specification to the enablement of the claims, because it is not clear that the results on pages 56-57 are from treatment using the MEK proteases or small molecule MEK inhibitors, or both at the same time. Further, no disclosure of which small molecule inhibitor is used for the treatment is found in the specification, nor any actual treatment data using PD184352 alone is found. Further the specification lacks guidance on the dosage necessary for the treatment, and schedules of treatment, using the small organic molecule PD184352.

Further, although PD184352 induces apoptosis of human melanoma cells *in vitro*, characteristics and responses of cells in culture to drugs are different from characteristics and responses of cells to drugs in primary cancer tissues, due to homeostasis which is absent in *in vitro* conditions. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results

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obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactual antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactual chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. Further, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, petri dish cancer is a poor representation of malignancy, with characteristics

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profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary - type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

This is particularly true, in view that only a certain specific level of reduction of ERK1/2, enzymes of the MAPK pathway, but not any level of reduction of ERK1/2, seems to be correlated with apoptosis, and thus due to possible homeostasis regulation, one cannot predict that PD184352 would reduce ERK1/2, enzymes of the MAPK pathway, to a specific level in melanoma cells *in vivo*, effective for inducing apoptosis of human melanoma cells.

Moreover, one cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or

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animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method comprising the administration of PD184352 would function as claimed. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method comprising the administration of PD184352 would function as claimed. . In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have

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been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

Therefore, it is unpredictable that PD184352 could induce apoptosis of melanoma cells, or killing melanoma cells or induce antitumor response in a patient.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

If Applicant could overcome the above 112, first paragraph rejection, claims 9 (b), 13, 14, 15 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing an antitumor response in a mammal having melanoma, comprising administering an inhibitor of the MAPK pathway, which inhibitor is cytotoxic to melanoma cells, thereby inducing a partial antitumor response, does not reasonably provide enablement for a method for inducing an antitumor response in a mammal having melanoma, administering an inhibitor of the MAPK pathway, which inhibitor is cytotoxic to melanoma cells, thereby inducing a "complete antitumor response". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

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Claims 9 (b), 13, 14, 15 are drawn to a method for inducing an antitumor response in a mammal having melanoma, administering an inhibitor of the MAPK pathway, which inhibitor is cytotoxic to melanoma cells, thereby inducing a complete antitumor response that is characterized by the "disappearance of all evidence of melanoma disease for at least one month."

The specification discloses that treatment of melanoma patients with small molecule inhibitors results in 86% patients having partial remission or less than partial remission (p.56-57). There is no disclosure concerning whether any of these treated patients have a complete antitumor response that is characterized by the "disappearance of all evidence of melanoma disease for at least one month."

One cannot extrapolate the teaching in the specification to the claims, because the degree of efficacy of a drug is not predictable, unless tested. Thus although treatment of melanoma patients with small molecule inhibitors results in 86% patients having partial remission or less than partial remission, one cannot predict that treatment of melanoma patients with PD184352 would result in a complete antitumor response that is characterized by the "disappearance of all evidence of melanoma disease for at least one month."

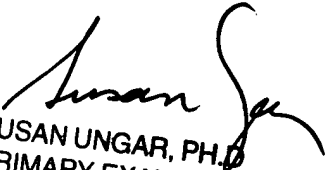
In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.


SUSAN UNGAR, PH.D.
PRIMARY EXAMINER

MINH TAM DAVIS

May 28, 2003